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10/600,862	06/20/2003	Todd Zankel	30610/39383	8574

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/600,862	ZANKEL ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004 and 18 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-24* is/are pending in the application.

4a) Of the above claim(s) *10-13,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 17-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *10-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/21/04 8 2/14/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. The amendments filed 16 December 2004 and 18 March 2005, and the declaration filed 16 December 2004 have been entered. Applicant has cancelled claims 1 – 9, amended claim 10, presented new claims 14 – 24, and requested withdrawal of claims 11 – 13. It is noted that in the amendment filed 16 December 2004 p. 6 indicates that claims 14 – 28 have been presented, but the versions of the claims filed both 16 December 2004 and 18 March 2005 end at claim 24. It is assumed that the remarks filed 16 December 2004 contain a typographical error and that there are only 24 claims. Claims 10 – 24 are pending in the instant office action.

Election/Restrictions

2. Applicant's election with traverse of Group I in the reply filed on 16 December 2004 is acknowledged. Applicant's further election of alpha-glucoisdase in the reply filed 18 March 2005 is acknowledged. The traversal is on the ground(s) that:

a) Once product claims have been found allowable methods claims directed to the products should be rejoined.

b) The restriction requirement mailed 14 January 2005 is improper, and should be replaced with an election of species requirement instead.

This is found persuasive in part, as follows.

a) Applicant retains the right to have process claims rejoined should any product be found allowable, as specifically enumerated on pp. 4 – 5 of the restriction requirement mailed 24 November 2004. However until product claims are found allowable, all methods claims shall remain withdrawn. The response of 16 December 2004 does not point out reasons why applicant believes the restriction between product and methods claims is improper.

b) Applicant cites MPEP § 803.02 and argues that restriction of Markush-types claims is improper. This reasoning is persuasive, as the agents recited in the claims share a common core structure, namely RAP, and a common functionality, namely targeting to lysosomes. However MPEP §803.02 also states that:

> In applications containing claims of that nature, the examiner may require a provisional election of a single species prior to examination on the merits. The provisional election will be given effect in the event that the Markush-type claim should be found not allowable. Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable over the prior art, examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species

patentably distinct from the elected species held withdrawn from further consideration.

Thus, the restriction requirement is hereby withdrawn and replaced with election of species. Since applicant has already elected alpha-glucosidase, the same election stands. Applicant is advised that claim 14 is being examined to the extent that it reads on RAP conjugated to alpha-glucosidase.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 10 – 13, 15, and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 16 December 2004 and 18 March 2005.

4. Claims 14 and 17 – 24 are under examination in the instant office action.

Information Disclosure Statement

5. The information disclosure statement filed 16 February 2005 lists the International Search Report. While the report itself has been considered, the citation is not in the proper format for publication on the face of a patent.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 14 and 17 – 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for human Receptor Associated Protein (RAP), with the sequence enumerated in SEQ ID NO:1, conjugated to enzymes deficient in lysosomal storage diseases, wherein the conjugation is either by covalent bonds or by amino acid linkers or by linkers up to about 30 atoms long, does not reasonably provide enablement for RAP proteins from other species, or for derivitization of either the RAP or the enzyme with a polyethylene glycol moiety. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

The claims are drawn to conjugates between RAP and enzymes that are deficient in lysosomal storage diseases. The term "Receptor Associated Protein" is not limited by either structure or function. While there appears to be agreement in the art as to which genes are RAPs, the sequence homology between them is so low that it is unclear that they will all function identically. Figure 13 of the instant application presents an alignment, at the amino acid level, of human, mouse, rat, chicken, zebrafish, fruit fly, and mosquito RAP. Across species, there are many significant gaps, insertions, deletions, and mismatches.

The work of Medved et al. (1999. J Biol Chem 274:717-727) is particularly informative. Working with human RAP, Medved et al. found that the molecule is made up of four domains, from residues 1 – 92, 93 – 163, 164 – 216, and 217 – 323 (see p. 727, final paragraph). Medved et al. also teach that sequence similarity is not an appropriate method to deduce function of this protein (see p. 726, first paragraph of Discussion), as it leads to an erroneous prediction of the number of domains. Medved et al. teach that domains 1, 2, and four all are involved in binding of RAP to the receptor LRP, and since the instant invention is based upon RAP's role as a LRP ligand (specification, p. 3, lines 27) clearly these regions are necessary for the invention to work. However, the human sequence is not identical to any of the other species in these regions, as evidenced by Figure 14, and there is no requirement in the claims that any particular region be present in the RAP molecule.

The claims are broad, in that they are directed to any RAP. The nature of the invention, construction of fusion proteins, is complex. The art, as it is drawn to relationships between protein sequence and function is unpredictable. The only working examples of RAP-conjugated enzymes involve the human sequence. Therefore, it would require undue experimentation on

the part of a skilled artisan to make and use the invention commensurate in scope with the claims.

8. Claims 14 and 17 – 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims recite compounds comprising Receptor-Associated Protein (RAP). While the sequence of human RAP is known and disclosed in the specification as SEQ ID NO:1, the claims as written are drawn to a genus which is not fully described in the specification. The claims encompass the human sequence, as well as the sequences of every other species of animal that has this gene, and are sufficiently broad to include not just the protein sequence but nucleic acids, as well as regulatory and untranslated regions. The claims are akin to example 6 of the Revised Interim Written Description Guidelines Training Materials, available on the USPTO'S web site at http://www.uspto.gov/web/offices/pac/writtendesc.pdf, directed to the recitation of genes. The claims are drawn to genera of nucleic acid and protein sequences, including those with regulatory elements, untranslated regions, allelic variants, mutation sequences, and sequences across all species as encompassed by the terms "Receptor Associated Protein." The art teaches that the interactions of untranslated regions of genes is complex and gene-specific (see Mazumder et al., 2003. Trends in Biochemical Sciences 28:91-98, particularly the paragraph that spans pp. 91 - 92). One of skill in the art would not be able to know, based on the disclosure, which elements are necessary for the construction of the agents claimed herein.

9. Claims 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 20 recites the limitation of 5 to 50 amino acids. On p. 7 of the remarks filed 13 December 2004, applicant directs the examiner's attention to pages 32 – 33 of the specification as providing support for claim 20. However, the examiner is unable to find support for the specific range recited in claim 20 on those pages. Page 31, lines 3 – 5 provides support for

linkers up to about 30 *atoms* long. Page 31, lines 25 – 28, provides support for certain numbers of molecules of an active agent added to the RAP by means of a conjugation reaction.

Claim 21 is directed to PEGylation of the agent. On p. 7 of the remarks filed 13 December 2004, applicant directs the examiner's attention to page 33 of the specification as providing support for claim 21. However, the examiner is unable to find support for the PEGylation, derivitization of the agent, or polyethylene glycol on page 33. Page 33, line 1, recites the term "derived" but this refers to the source of the protein, not "derivitized" i.e. modification of the protein.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 14, 17, 19, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al. (1999. Clinical Genetics 55:389 – 394) in view of Czekay et al. (1997. Molecular Biology of the Cell 8:517-532, cited on the information disclosure statement filed 27 May 2004).

The claims are drawn to compounds comprising RAP and human alpha-glucosidase. Russell et al. teach fusion proteins (i.e. two proteins coupled by an amino acid linker or a peptide bond) and their use in disease states. Particularly, Russell et al. teach that fusion proteins can be engineered to deliver proteins to specific subcellular compartments, and that there is a long-standing need for such targeted delivery (see p. 391, first complete paragraph). Russell et al. point out that enzyme replacement is an important treatment for lysosomal storage diseases (p. 390, second column) and indicate that alpha glucosidase is a treatment of Pompe disease p. 390, Table 2). Russell et al. contemplate pharmaceutical compositions, as the entire paper is directed toward treatment of disease with recombinant proteins. Russell et al. do not teach agents comprising RAP.

Czekay et al. teach RAP fusion protein, specifically RAP fused to GST (see p. 518, second column). Czekay et al. further teach that RAP is rapidly delivered to lysosomes (see abstract, as well as p. 520, second column). It would have been obvious to one of ordinary skill

in the art to make a fusion protein between RAP and human alpha-glucosidase, with a reasonable expectation of success. Russell teaches the need for fusion proteins with a targeting moiety to bring therapeutic components to specific intracellular locations, and specifically mentions Pompe disease, which is characterized by a lack of functional alpha-glucosidase in the lysosome. Czekay teaches a fusion protein comprising RAP and shows it is targeted to the lysosome. The motivation would be to target the enzyme to the appropriate subcellular location, as suggested by Russell.

12. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell and Czekay as applied to claim 14 above, and further in view of Blattler et al. (1985. Biochem 24:1517-1524). Neither Russel nor Czekay teach direct covalent linkage of the two proteins. Blattler et al. teach acid-labile protein cross-linking reagents for direct conjugation of peptides. Czekay et al. teach that the late endosome has a pH of 5.5 (see abstract), and Blattler et al. teach that their method results in a linkage that is stable until the pH is between 4 and 5 (p. 1518, first column, last sentence). It would have been obvious to one of ordinary skill in the art to use the direct conjugation method of Blattler et al., with a reasonable expectation of success. A motivation would be to join the two components together and keep them together in the relatively low pH of the late endosome, as suggested by Czekay (see abstract).

13. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell and Czekay as applied to claim 14 above, and further in view of Davis et al. (U.S. Patent 6,072,041, issued 6 June 2000, filed 24 October 1997). Neither Russell nor Czekay teach amino acid linkers from 5 to 50 residues in length. Davis et al. teach fusion proteins for targeted drug delivery, using therapeutic components and targeting components (see column 2, lines 5 – 9). Davis et al. teach that the two components can joined by a linker of less than 10, 20, 30, 40, or 50 amino acids (column 2, lines 19 – 20), and further teach that any therapeutic component may be used (column 2, line 40). It would have been obvious to use a linker of between 5 to 50 amino acids, with a reasonable expectation of success, as lengths within this range are explicitly recited as preferred embodiments by Davis.

14. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell and Czekay as applied to claim 14 above, and further in view of Reddy (2000. Annals of Pharmacology 34:915-923). Neither Russell nor Czekay teach polyethylene glycol (PEG) derivitization of polypeptides. Reddy teaches that PEG may be attached to proteins either at a single site or multiple sites (see p. 919, end of first column), and that doing so confers

advantages for delivery of pharmaceuticals, including increased half-life, decreased fluctuation of plasma concentration, enhanced in vivo activity, decreased toxicity and immunogenicity. These advantages and others are listed in Table 1, p. 917. It would have been obvious to one of ordinary skill in the art to derivatize either RAP or the enzyme with PEG, with a reasonable expectation of success. A motivation would be to increase the stability of the protein, or any of the other advantages listed in Table 1 of Reddy.

15. Claims 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell and Czekay as applied to claim 14 above, and further in view of either White et al. (U.S. Patent 5,962,266, issued 5 October 1999, filed 2 April 1997) or Strom et al. (U.S. Patent 6,165,476, issued 26 December 2000, filed 10 July 1997). Neither Russel nor Czekay teach pharmaceutical compositions comprising fusion proteins prepared for administration either via inhalation or intravenously. White teaches pharmaceutical compositions comprising fusion proteins, and teaches the preparation of said compositions for intravenous infusion (column 18, lines 35 – 45). White further teaches that the pharmaceutical compositions can be administered by inhalation (column 18 lines 30 – 33). Strom et al. teach pharmaceutical compositions comprising fusion proteins, and their preparation for intravenous and inhaled administration (column 13, lines 14 – 20). Strom further teaches that pharmaceutical compositions prepared in this manner are advantageous in that they are non-toxic to recipients at the dosages and concentrations employed (column 13, lines 6 – 7). It would have been obvious to one of ordinary skill in the art to prepare a pharmaceutical composition comprising a fusion protein for either intravenous or inhalation administration, as taught by both Strom and White, with a reasonable expectation of success. A motivation to do so would be to gain the advantage of minimal toxicity to recipients, as taught by Strom.

Double Patenting

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 14, 17 – 20, and 22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 – 16 of copending Application No. 10/812,849, in view of Russell et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because in both cases the claims are drawn to receptor-associated protein coupled to agents of interest. In the instant case, the scope of the claims is limited to RAP. In the '849 application the claims are drawn to megalin-binding agents generically (claims 1 – 7 and 10 - 16), or to RAP, either as part of a Markush group (claim 8), or specifically (claim 9). It is acknowledged that alpha-glucosidase it not specifically enumerated in any of the claims of the '849 application. However, the generic claims of the '849 are sufficiently broad to reasonably include RAP coupled to alpha-glucosidase, and further dependent claims of the '849 application include methods of treating lysosomal storage diseases by administration of the megalin-binding agents coupled to therapeutic agents used in the treatment of said diseases (see claims 24 – 26), and Pompe disease is specifically enumerated as one of the diseases in claim 26.

Pompe disease is characterized by decreased activity of alpha-glucosidase, as explained by Russell et al. (see particularly Table I on p. 390). Claims 1 – 16 of the '849 application are sufficiently broad to encompass RAP conjugated to alpha-glucosidase. In light of the disclosure of the '849 application, and the teachings of Russell et al., it would be immediately obvious to one of ordinary skill in the art would to make a fusion protein between RAP and alpha-glucosidase. Russell et al. teach fusion proteins for treatment of lysosomal storage diseases, and teach that Pompe disease is characterized by decreased activity of alpha-glucosidase, and the '849 application teaches RAP conjugated to enzymes deficient in lysosomal storage diseases, including Pompe disease. A motivation would be to target the enzyme to the lysosome, thereby treating the disease, as suggested by Russell et al.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

17. No claim is allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (571) 272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 2, 2005

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